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webinar series

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Zoster Vaccines in Older Adults
September 21, 2017

The Clinical Problem . . .

- 78 year old man in good health working as the CEO of a company . . .

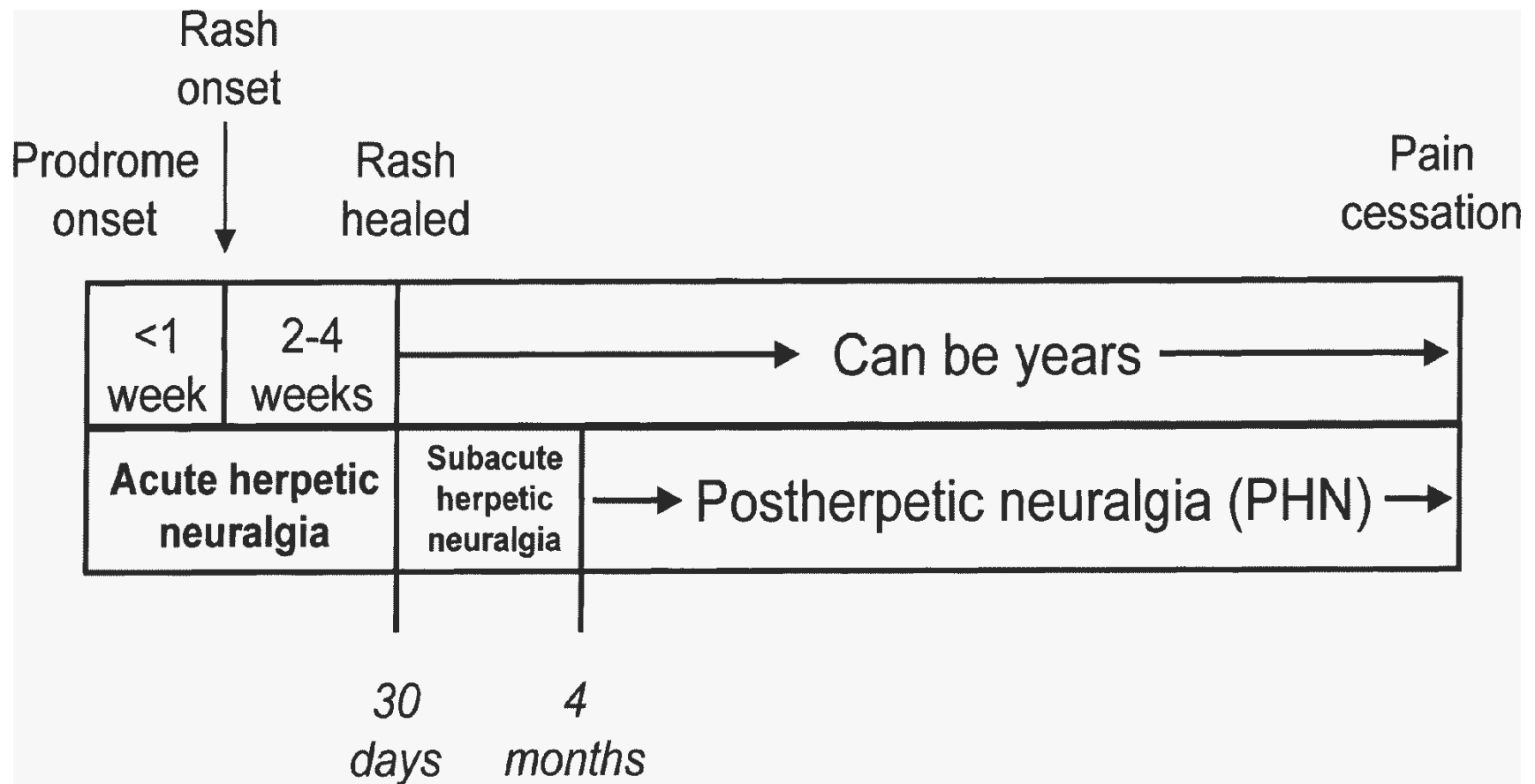
. . . In the Patient's Words

I've had postherpetic neuralgia for . . .
from the start of the shingles until now, I
don't know, it's been 50 some days.

The pain has worn me down to the last
straw. I am at the end of my line. I got to
have somebody do something.

I desperately, desperately need help. I
don't know how much longer I can take it.

Pain is the Cardinal Problem Posed by Herpes Zoster in Older Adults -- *Acute and Chronic Pain*

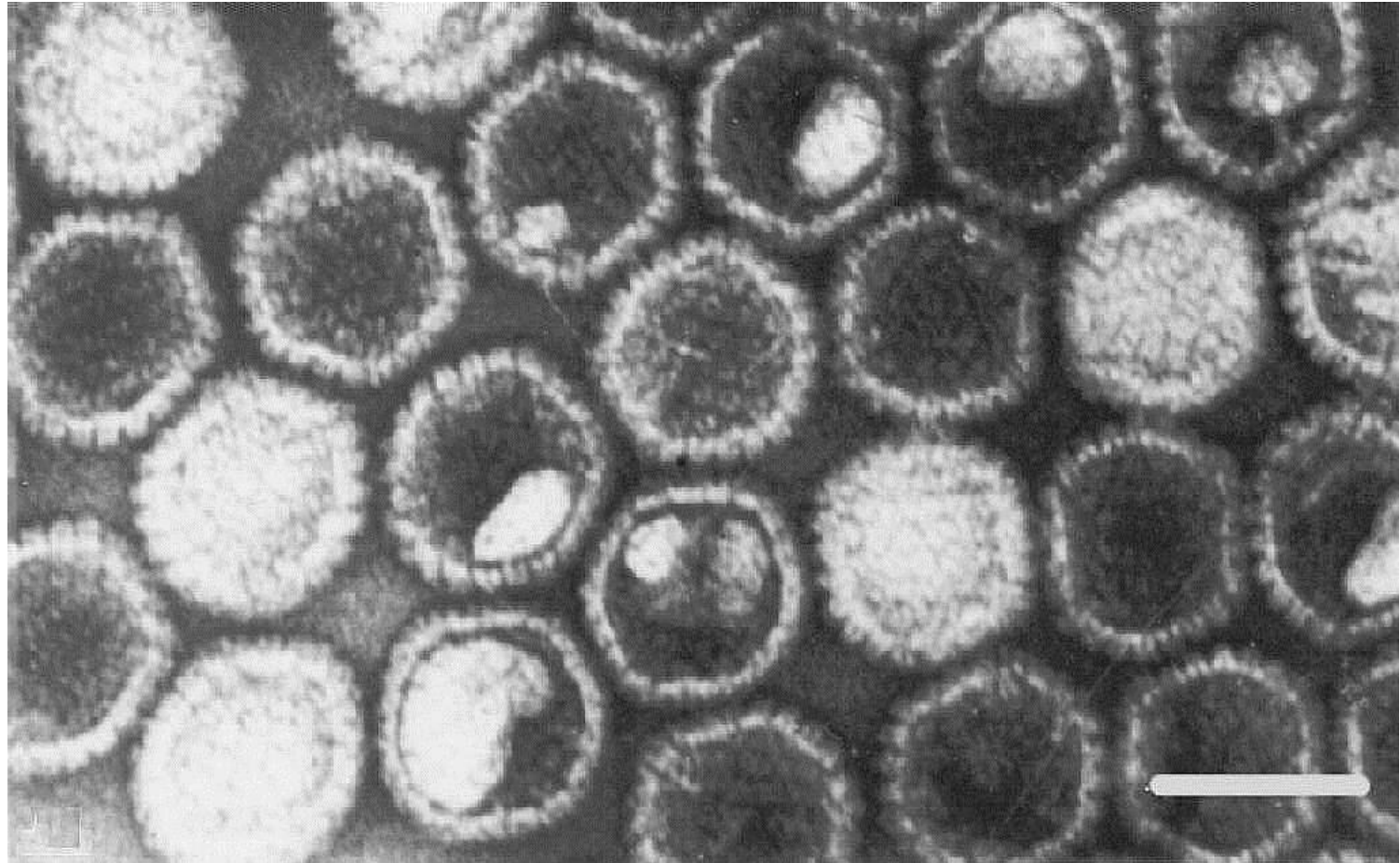


Acute and Postherpetic Neuralgia

Adverse Impact on Multiple Domains of Health

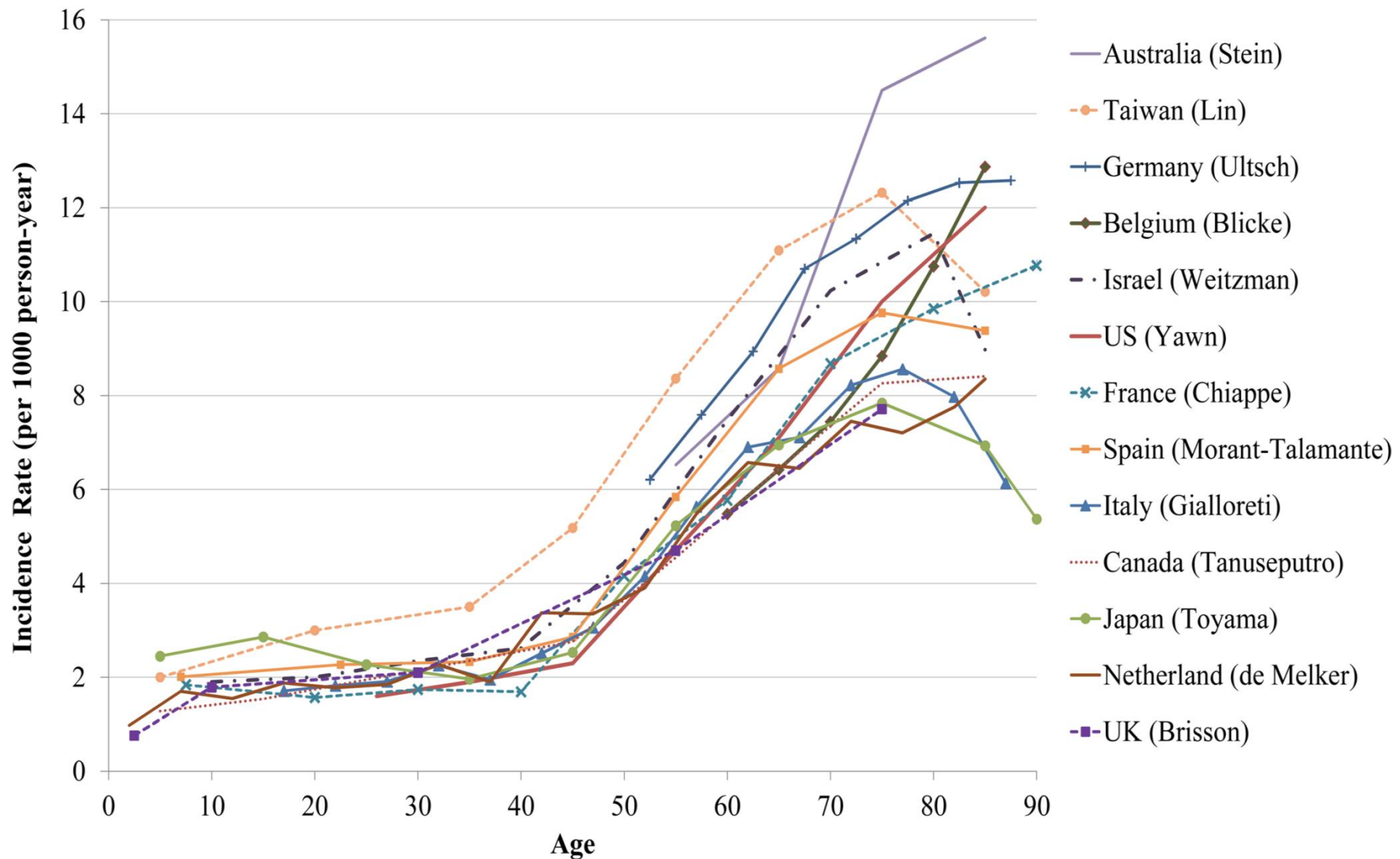
Physical	Psychological
<ul style="list-style-type: none"> • Fatigue • Anorexia • Weight loss • Physical inactivity • Insomnia 	<ul style="list-style-type: none"> • Depression • Anxiety • Difficulty concentrating
Social	Functional
<ul style="list-style-type: none"> • Decreased social gatherings • Change in social role 	<ul style="list-style-type: none"> • Interfere with basic and instrumental activities of daily living <ul style="list-style-type: none"> – Dressing, Bathing, Eating, Mobility – Travelling, Cooking, Housework, Shopping

Electron Micrograph of Varicella Zoster Virus (VZV)





Age and Incidence of Herpes Zoster





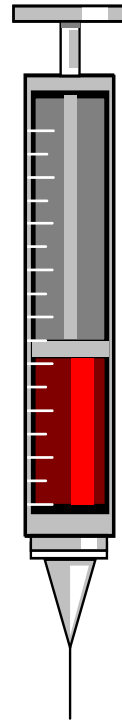
Strategies to Enhance Protection of Older Adults Against Vaccine-Preventable Diseases

- Improve Immune Response to Vaccines
 - Live, attenuated
 - Higher dose
 - Adjuvants
 - Conjugates
 - Subunit
 - DNA
 - Recombinant vector



Live Attenuated Zoster Vaccine

- Live, attenuated, cell-free preparation of Oka/Merck strain VZV
- Contains whole live virus, viral antigen and
- Neomycin, sucrose, gelatin, glutamate, inorganic salts



- Formulated to contain substantially more live virus and viral antigen than are contained in the varicella vaccine

Shingles Prevention Study

- *Design:* Randomized, double-blind, placebo-controlled, stratified by age, 60-69 and ≥ 70 years
- *Setting:* 22 US sites (16 VA and 6 university medical centers)
- *Participants:* 38,546 immunocompetent adults ≥ 60 years old
 - 19,270 zoster vaccine
 - 19,276 placebo

Shingles Prevention Study

- *Intervention:* One dose of live attenuated zoster vaccine or placebo
- *Outcomes:* Incidence of HZ and PHN and Pain Burden of Illness (BOI)

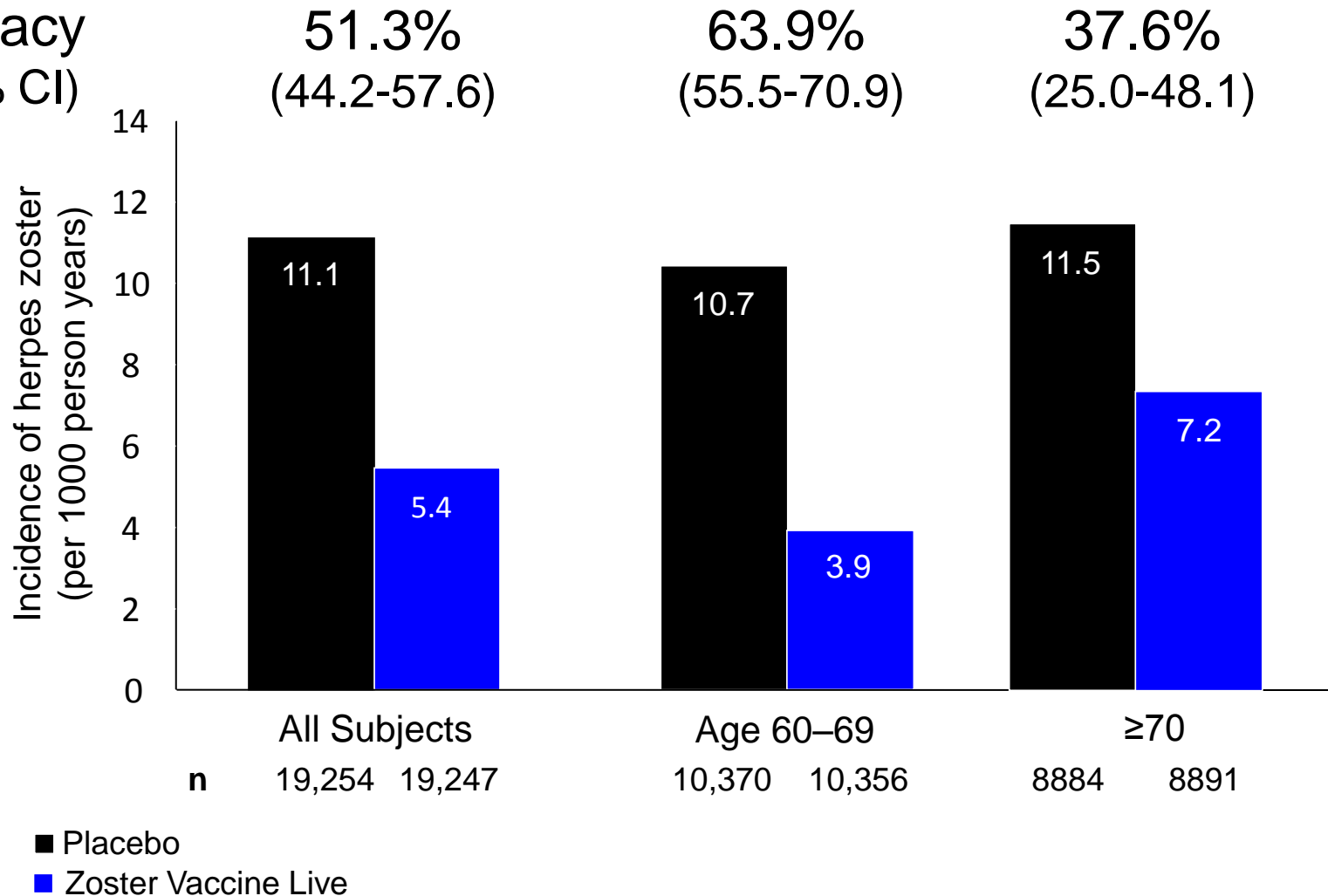


Oxman M et al. N Engl J Med. 2005;352:2271-2284

Efficacy of Live Zoster Vaccine

Incidence of Herpes Zoster

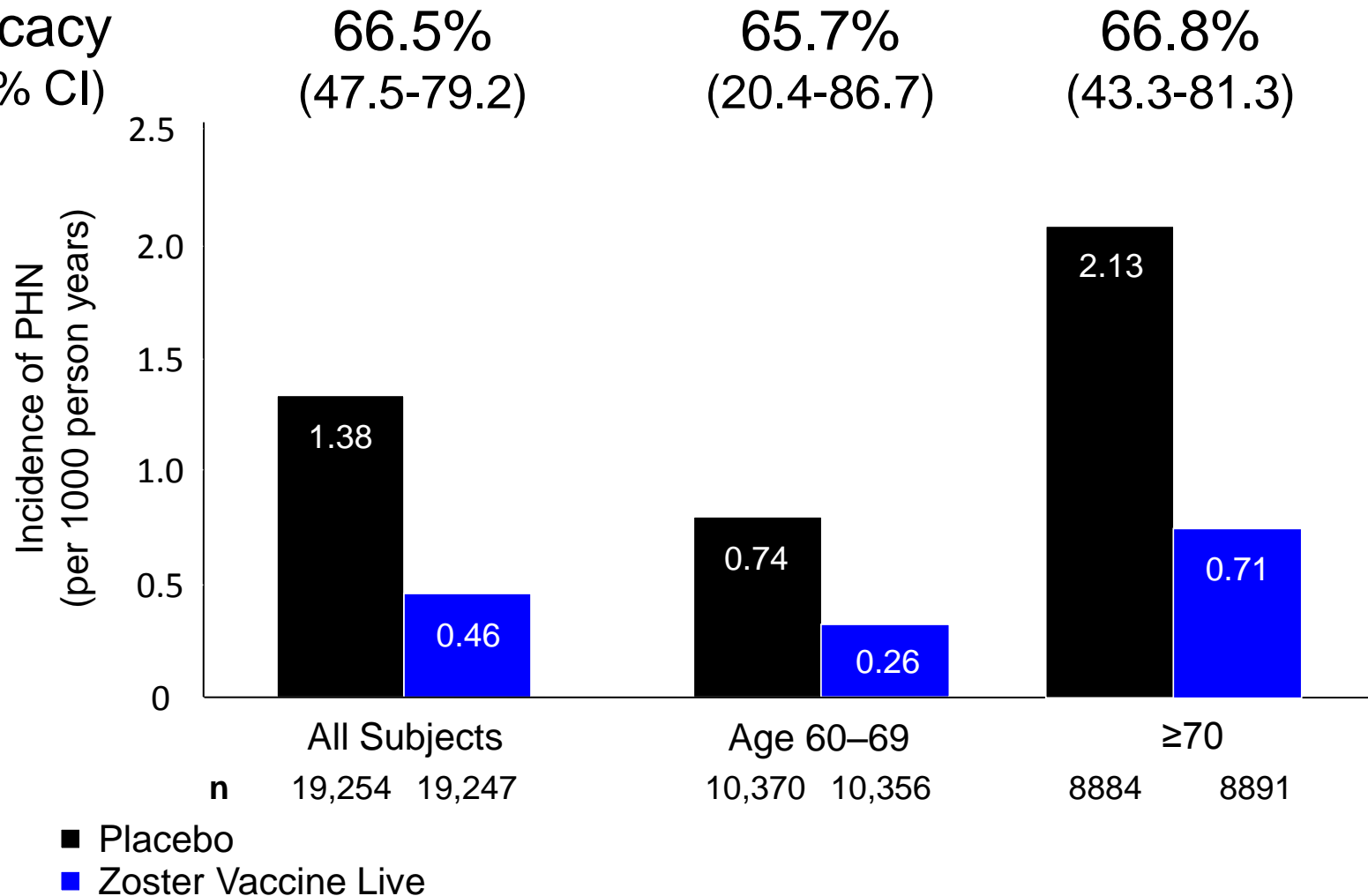
Efficacy
(95% CI)



Efficacy of Live Zoster Vaccine

Incidence of Postherpetic Neuralgia

Efficacy
(95% CI)



Figures 1 and 2 should be read with the footnotes that contain important general information and considerations for special populations.

Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

Vaccine	19–21 years	22–26 years	27–59 years	60–64 years	≥ 65 years
Influenza ¹	1 dose annually				
Td/Tdap ²	Substitute Tdap for Td once, then Td booster every 10 yrs				
MMR ³	1 or 2 doses depending on indication				
VAR ⁴	2 doses				
HZV ⁵				1 dose	
HPV–Female ⁶	3 doses				
HPV–Male ⁶	3 doses				
PCV13 ⁷					1 dose
PPSV23 ⁷	1 or 2 doses depending on indication				1 dose
HepA ⁸	2 or 3 doses depending on vaccine				
HepB ⁹	3 doses				
MenACWY or MPSV4 ¹⁰	1 or more doses depending on indication				
MenB ¹⁰	2 or 3 doses depending on vaccine				
Hib ¹¹	1 or 3 doses depending on indication				



Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

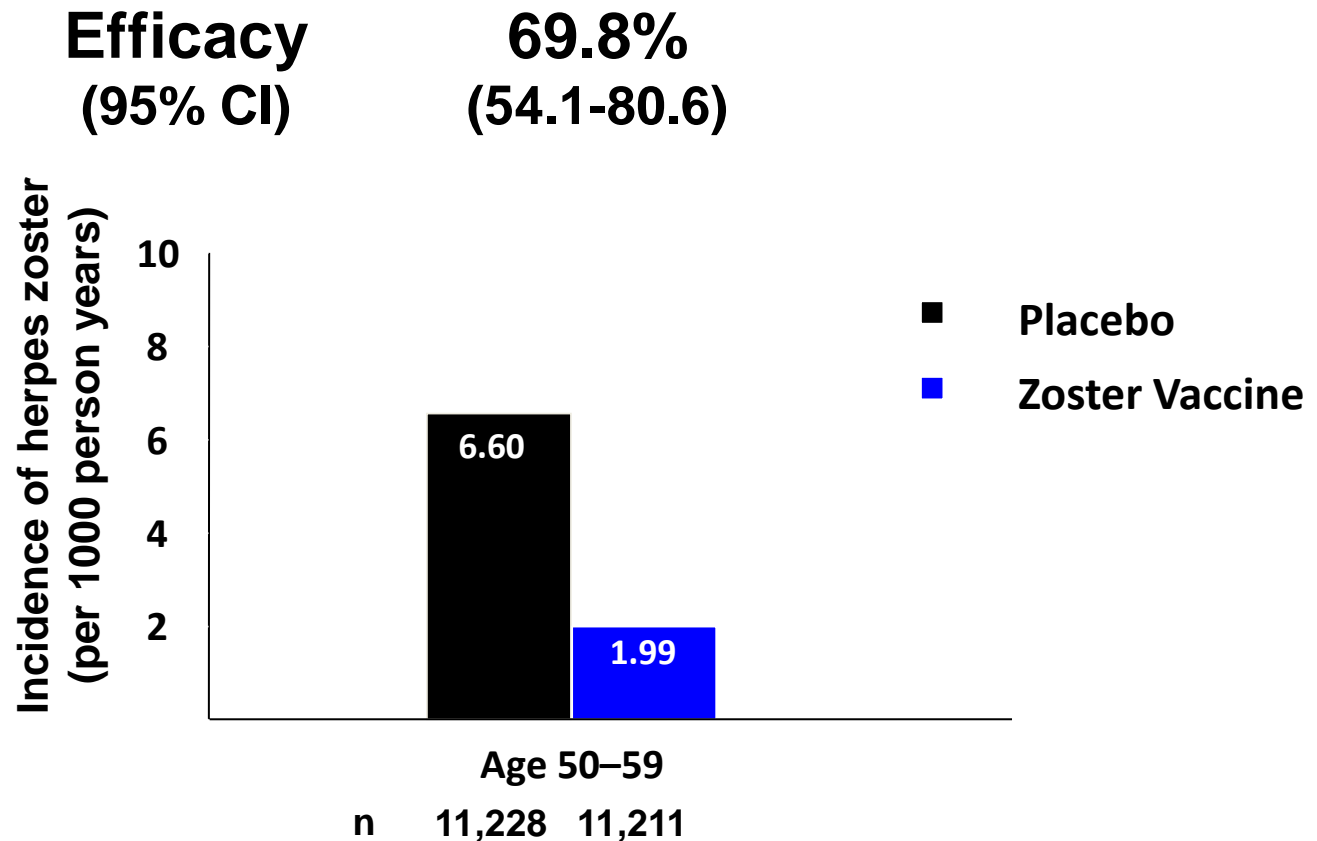


Recommended for adults with additional medical conditions or other indications



No recommendation

Effect of Zoster Vaccine on Incidence of Herpes Zoster in Persons 50-59 Years Old



How Persistent is the Effect of the Live Zoster Vaccine?

VA CSP #403B: The Short-Term Persistence Substudy*

- Follow-up 3.3 to 7.8 years
- Comparator: Placebo
- Vaccine Efficacy for HZ: 39.6%

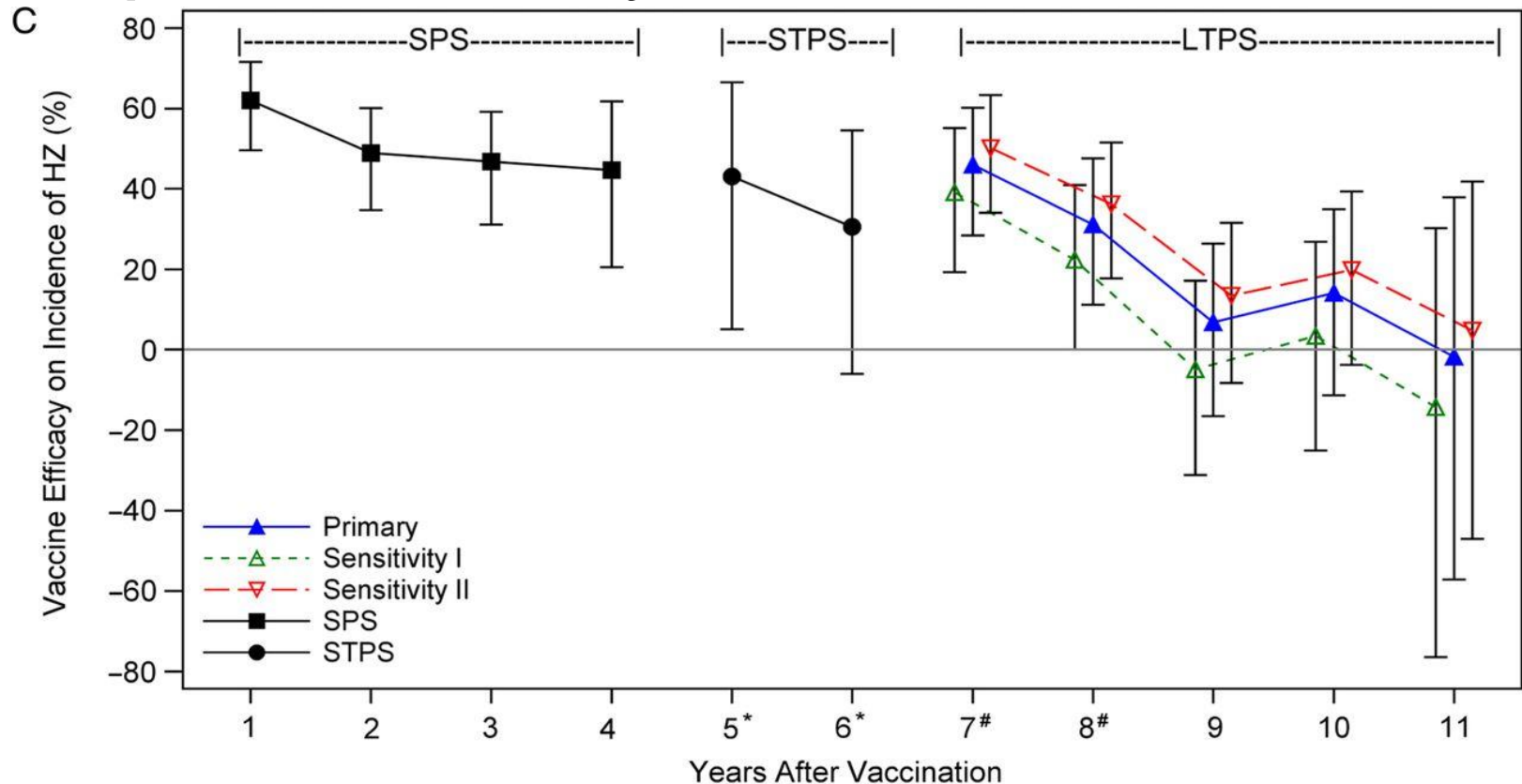
VA CSP #403C: The Long-Term Persistence Substudy**

- Follow-up 4.7 to 11.6 years
- Comparator: Historical controls
- Vaccine Efficacy for HZ: 21%

*Schmader KE et al. Clin Infect Dis 2012;55(10):1320–8

**Morrison V et al. Clin Infect Dis 2015;60:900-909

Efficacy of Live Zoster Vaccine on Herpes Zoster by Year After Vaccination



Primary					46.0	31.1	6.8	14.1	-1.7
Sensitivity I					39.1	22.4	-4.9	3.4	-14.2
Sensitivity II					50.2	36.2	13.4	19.9	4.8
SPS	62.0	48.9	46.8	44.6					
STPS					43.1	30.6			

SPS = Shingles Prevention Study; STPS = Short-Term Persistence Substudy; LTPS = Long-Term Persistence Substudy

Morrison et al. Clin Infect Dis. 2015;60:900-909; Schmader KE et al. Clin Infect Dis 2012;55:1320-8

So . . .What about a booster dose?

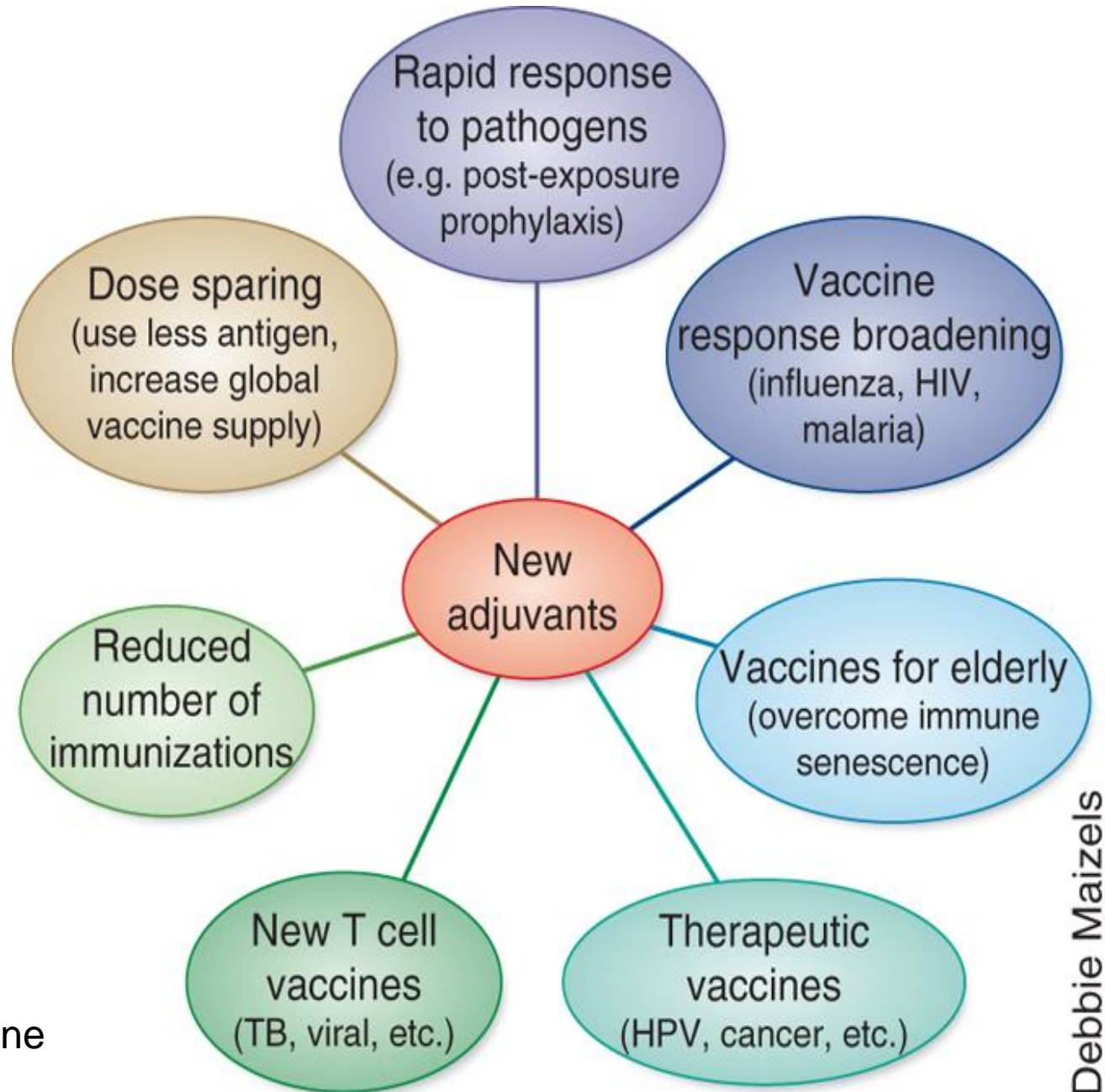
- Live zoster vaccine administered as a booster dose ≥ 10 years after first dose in individuals ≥ 70 years old
 - Significantly increases immunity to VZV
 - Increase in VZV immunity in the booster dose group is significantly higher than matched first-time immunization group for one year after immunization
- But clinical significance of immunological findings is unknown . . .
 - ACIP does not recommend a second dose of live zoster vaccine at this time

Strategies to Enhance Protection of Older Adults Against Vaccine-Preventable Diseases

- Improve Immune Response to Vaccines
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 - Higher dose
 - **Adjuvants**
 - **Subunit**
 - Conjugates
 - DNA
 - Recombinant vector



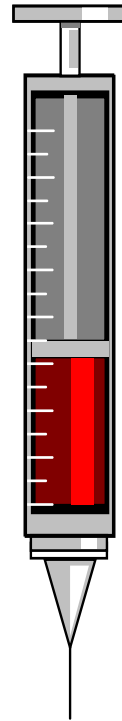
An adjuvant is a substance that potentiates the immune response to an antigen



Debbie Maizels

Adjuvanted Zoster Subunit Vaccine

- Recombinant VZV glycoprotein E (gE) antigen and
- Liposome-based AS01b adjuvant
- Liposome is a spherical vesicle having at least one lipid bilayer



- AS01b adjuvant system contains:
- monophosphoryl lipid A (MPL) and
- saponin, a phytochemical (*Quillaja* s...



Adjuvanted Zoster Subunit Vaccine Trial ZOE-50

- *Design:* Randomized, double-blind, placebo-controlled in persons ≥ 50 years old, stratified by age, 50-59, 60-69, 70-79, ≥ 80
- *Setting:* Multiple centers in North America, Europe, Latin America, Asia-Pacific
- *Participants:* 14,759 immunocompetent adults
 - 7344 zoster vaccine
 - 7415 placebo

Adjuvanted Zoster Subunit Vaccine Trial ZOE-50

- *Intervention:* 2 doses of subunit zoster vaccine or placebo at 2 month intervals
- *Outcomes:* Incidence of HZ and PHN



Efficacy of Adjuvanted Zoster Subunit Vaccine ZOE-50

Vaccine (n=7344)		Placebo (n=7415)		Vaccine Efficacy % (95% CI)
HZ Cases (n)	Incidence per 1000 person-yrs	HZ Cases (n)	Incidence per 1000 person-yrs	
6	0.3	210	9.1	97.2 (93.7-99.0)

ZOE-50 Adverse Events and Reactogenicity

Reactogenicity Subgroup Within 7 Days After Vaccination

Variable	Vaccine % (95% CI)*	Placebo % (95% CI)*
Any adverse event	84.4 (83.3-85.5)	37.8 (36.4-39.3)
-Grade 3 [†] vaccination related	15.6 (14.5-16.7)	1.9 (1.5-2.3)
Injection site reaction	81.5 (80.3-82.6)	11.9 (11.0-12.9)
-Grade 3	9.5 (8.7-10.4)	0.4 (0.2-0.6)
Systemic reaction	66.1 (64.7-67.6)	29.5 (28.2-30.9)
-Grade 3	11.4 (10.5-12.4)	2.4 (2.0-2.9)

Vaccine n = 4460, Placebo n = 4466

[†]Grade 3 – prevented normal activity

ZOE-50 Adverse Events and Reactogenicity

Total Cohort Throughout Study Period

Variable	Vaccine % (95% CI)*	Placebo % (95% CI)*
Serious adverse event	9.0 (8.3-9.6)	8.9 (8.3-9.6)
Potential immune-mediated disease	1.0 (0.8-1.3)	1.3 (1.0-1.5)
Death	2.2 (1.9-2.5)	2.3 (1.9-2.6)

*Vaccine n = 7698, Placebo n = 7713

Efficacy of Adjuvanted Zoster Subunit Vaccine ZOE-70

Vaccine (n=6541)		Placebo (n=6622)		Vaccine Efficacy % (95% CI)
HZ Cases (n)	Incidence per 1000 person-yrs	HZ Cases (n)	Incidence per 1000 person-yrs	
23	0.9	223	9.2	89.8 (84.2-93.7)

US Vaccination Coverage among Older Adults for Zoster Vaccine, 2015

Vaccine	Coverage (%)
Zoster, ever	31